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THE TREATMENT OF STOKES-ADAMS SEIZURES*

Stokes-Adams seizures, as originally defined by Stokes in 1846,[1] consisted of syncopal attacks and convulsive seizures in patients with slow heart rates. Since electrocardiograms have been taken during such attacks, the following cardiac mechanisms, either alone or in combination, have been observed: (*a*) prefibrillatory type of ventricular tachycardia or ventricular flutter; (*b*) ventricular fibrillation; (*c*) complete cardiac standstill; and (*d*) ventricular asystole with maintenance of auricular beating.[2] In a broad sense, these seizures may result from any alteration in cardiac mechanism which results in a sudden drastic reduction in the cardiac output and consequently in the cerebral blood flow, *e.g.*, following the sudden onset of a slow heart rate or marked acceleration of the heart beat. Essentially the syncopal attacks or convulsive seizures which typify this syndrome are due to failure of the brain to receive an adequate blood supply for a period of three to nine seconds, or longer.

These seizures occur under the following conditions: 1) In their more typical form, during the transition from partial to complete A.V. block. 2) During the maintenance of complete A.V. heart block. Because of the instability of the cardiac pacemaker in this state, such episodes may occur spontaneously; however, they are frequently precipitated by emotion and excitement and may be induced by epinephrine and anoxia. 3) Less common is their appearance in patients with normal sinus rhythm, where the mechanism may be transient ventricular flutter-fibrillation and more rarely cardiac arrest (in association with aortic stenosis, hyperpotassemia and other less clearly defined states).[3] 4) In patients with the cardio-inhibitory type of carotid sinus syncope, vagal stimulation due to various factors results in episodes of ventricular standstill. Parasympathetic drugs, *e.g.*, digitalis, will induce such episodes in the group with normal sinus rhythm, as well as in patients with auricular fibrillation. 5) Quinidine, procaine amide and potassium may also be implicated by their depression of the cardiac pacemakers, in subjects with complete A.V. heart block and other states associated with slow heart rates.

Stokes-Adams seizures occur usually in the older age groups and in patients with arteriosclerotic heart disease. They are frequently observed in individuals with aortic stenosis, and are rarely associated with cardiovascular syphilis.

Problem of Therapy

The object of the therapy of Stokes-Adams seizures is to restore a normal or adequate cardiac rate and help to maintain the blood pressure and blood flow to the brain. This problem is complicated by a number of factors: (*a*) the variety of possible causes of the syndrome; (*b*) the lack of knowledge of the cardiac mechanism or mechanisms involved unless an electrocardiogram is taken during an actual attack; (*c*) the difficulty of treating certain cardiac mechanisms, such as ventricular fibrillation and flutter, even when they have been identified; (*d*) the fact that drugs which stimulate the cardiac pacemaker may also produce or increase irritability in various ventricular and nodal pacemakers.

Treatment of the Underlying Clinical State

Treatment of the underlying clinical state, if successful, may have a salutary effect in preventing subsequent seizures. Cessation of attacks may be observed in the following conditions: 1) With the healing of an acute myocardial infarction, the complete A.V. block that has occurred tends to revert to normal sinus rhythm in two to three days. 2) Myocarditis (of rheumatic or other etiology) may occasionally precipitate seizures, and with improvement of this state the attacks cease. 3) Following successful surgical treatment of aortic stenosis, the syncopal attacks often disappear. 4) Removal of the causative factor, *e.g.*, a diverticulum of the esophagus, interruption of a reflex pathway producing carotid

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sinus syncope, or omission of digitalis, which is a parasympathetic stimulant, may result in improvement. 5) In rare cases, treatment of syphilis may resolve a gumma which has interrupted the A.V. nodal pathway and has been the causative factor of these seizures.[4]

Prophylaxis

The prophylactic approach to the Stokes-Adams syndrome involves avoidance of those factors which tend to precipitate attacks. For example, patients with complete A.V. block are unable to respond to stress with an adequate increase in cardiac output and tend to develop Stokes-Adams attacks under these conditions. Strenuous exertion, emotional upsets, or other factors which tend to precipitate syncopal attacks should be avoided.

In symptomatic complete A.V. block or bradycardia, prophylactic treatment may be instituted by the selective use of the following drugs: vagolytic (atropine, Banthine), sympathomimetic (epinephrine, Isuprel), and molar sodium lactate. In the cardio-inhibitory type of carotid sinus syncope, the prophylactic use of sympathomimetic drugs may avoid these episodes by stimulating the cardiac pacemakers and counteracting vagal effects. Digitalis or other parasympathomimetic drugs in susceptible subjects of this kind should be avoided or given with caution.

Therapy During Attacks

The therapy of the attack is complicated by the varied mechanisms or combinations that are observed during these episodes. Several empiric measures are available, but a more rational plan of treatment can be instituted if an electrocardiogram is obtained during the attack.

In the therapy of Stokes-Adams seizures, two types of episodes are encountered: 1) The single or transient attack, where recovery is either spontaneous or the patient succumbs by the time he is seen by his physician. The effectiveness of therapy of this single episode is very difficult to evaluate. 2) With repeated episodes, if the patient is connected to the electrocardiograph, the exact mechanism of the seizures can be ascertained. Thus more adequate therapy can be planned and its effectiveness evaluated.

Direct, vigorous thumping on the precordium is particularly helpful in the presence of cardiac arrest or ventricular asystole. This simple method has restored ventricular contractions after cardiac standstill, and has kept patients alive for as long as twelve hours. It is an extremely useful temporary procedure, and gives the physician time to study the patient more thoroughly and prepare one of the more specific types of therapy outlined below.

Epinephrine. The dose and method of administration depends on the clinical situation. During cardiac arrest it may be administered by intracardiac injection (0.25 to 1 ml. of a 1:1000 solution). It should be emphasized that the patient may recover from the episode spontaneously, even as the injection is given. He may be having ventricular tachycardia, flutter or fibrillation, which may be irreversible or end in spontaneous recovery. In the latter group, epinephrine may be harmful. The patient may be having an episode of cardiac arrest, and in that case the administration of epinephrine may be lifesaving, although it may occasionally precipitate ventricular flutter or fibrillation. Cause and effect are singularly difficult to determine under these conditions. The mere pricking of the epicardium with a needle may sometimes stop the attack. Under such critical circumstances the physician, in panic, may do something which is harmful to the patient.

To maintain an adequate heart rate (30 to 40 beats per minute), and to prevent further seizures (particularly in a state of hypotension or shock), 0.2 to 0.3 ml. of a 1:1000 solution (diluted tenfold) of epinephrine may be given by slow drip, intravenously, under careful observation. Care should be exercised to avoid intravenous injection of epinephrine when subcutaneous or intramuscular injection will suffice.

Where the indications are less urgent, epinephrine may be given in a dose of 0.2 to 0.3 ml. subcutaneously every 1 to 2 hours, or may be given as a 1:1000 solution in oil (1.0 ml. intramuscularly) depending on the desired results.

Norepinephrine. Norepinephrine, or other vasopressor agents, may be administered in those patients in whom the restoration of the heart beat is associated with marked hypotension. While often efficacious in raising the blood pressure, the administration of these drugs often carries the danger of inducing ectopic rhythms.

Isuprel. Isuprel is extremely valuable in the management of Stokes-Adams seizures. In its action on the heart, Isuprel resembles epinephrine, but it is superior to the latter in some respects. For example, it is less likely to precipitate ventricular fibrillation and may be given when this arrhythmia is already established. Isuprel has occasionally proved effective in restoring a normal cardiac rate in the presence of ventricular extrasystoles and ventricular tachycardia.[5]

The drug is given by the following methods: sublingually in doses of 10 to 20 mg. every two hours, or as required; subcutaneously 0.2 mg. every six hours, or as indicated; or intravenously as a continuous infusion of 1 mg. Isuprel in 200 ml. of 5 per cent glucose in distilled water, or 4 ug. per cu. cm., at a rate of 9 to 200 drops per minute.

Other Sympathomimetic Drugs. To alleviate attacks occurring with moderate frequency, or

for more chronic use, the following sympathomimetic drugs may be given orally: ephedrine, 15 to 30 mg. (¼ to ½ grain), three to five times daily; Paredrine, 20 to 60 mg. (⅓ to 1 grain), three to five times daily. They are often combined with sedatives which counteract the nervous symptoms produced by these drugs.

Molar Sodium Lactate. In our experience, molar sodium lactate is an extremely valuable adjunct in the treatment of Stokes-Adams seizures, especially those associated with cardiac arrest.[6-9] This agent also has had a salutary effect in increasing cardiac rhythmicity in the presence of slow heart rates associated with hyperpotassemia and other conditions, and in the restoration of cardiac beating during cardiac arrest. It is difficult to evaluate the efficacy of a particular form of therapy for isolated Stokes-Adams seizures, since they often spontaneously cease. However, in patients with repeated Stokes-Adams episodes occurring within the space of a few hours, particularly when they present a relatively uniform pattern, character and duration, the effect of intravenous drug therapy can be judged with much greater reliability. In 7 patients out of a group of 10, molar sodium lactate was successful in restoring ventricular beating during many and repeated trials (in the majority of cases, 10 or more trials). With recurring episodes of ventricular standstill, the rapid infusion of molar sodium lactate consistently restored ventricular beating.[9]

Molar sodium lactate is most effective when given promptly, preferably within one to two minutes after the onset of the attack. The dose and rapidity of administration varies considerably, depending upon the type of attack and the period in which the patient is seen. If the patient is in extremis, following a relatively long period of cardiac standstill, 40 to 80 ml. may be given rapidly by vein in order that some of the infusion may reach the heart. *In other milder episodes of relatively short duration, where the need is not so urgent, smaller doses (10 to 20 ml.) may be given at one time.* After this, the solution should be administered as an intravenous infusion at the rate of 60 to 150 drops per minute, the exact rate and amount depending on the effects observed. As the ventricular rate increases, the infusion should be slowed down. When it becomes apparent that the pacemaker is spontaneously maintaining a satisfactory rate and the episodes of cardiac arrest have been abolished, it should be stopped. This infusion should be given under electrocardiographic control in order to determine the nature of the cardiac mechanism and the results of the infusion. A total of between 240 ml. within 30 minutes and 1000 ml. in six hours have been given for repeated episodes without untoward effects. Usually, however, smaller doses are required.

In subjects who experience occasional Stokes-Adams episodes, long-acting sympathomimetic drugs, *i.e.*, ephedrine or Isuprel, are the preferred method of treatment. We have recently been using oral molar sodium lactate (90 ml., *q.i.d.*) with promising results in an attempt to prevent and/or abort these occasional attacks.

Occasionally, various measures are employed to increase the rate of the ventricular pacemaker in asymptomatic complete A.V. block (*i.e.*, a slow heart rate without the manifestation of syncopal attacks). The use of such agents in complete A.V. block belongs in a different category from that in cardiac arrest, and merits some discussion. Patients with complete A.V. block are especially subject to ectopic rhythms because of areas of increased or decreased irritability in the heart muscle. The nodal or idioventricular pacemaker is notoriously unstable and any factor that increases cardiac work, such as the rapid infusion of fluid or hypertonic solutions (molar sodium lactate), might precipitate ectopic rhythms of various types. This is particularly likely when there are ectopic beats in the control tracing. The ventricular rate increased in 9 patients of this type (53 per cent); however, extrasystoles were produced or increased by molar sodium lactate in 5 subjects (29 per cent).[9] *We do not recommend molar sodium lactate for routine use in cases of asymptomatic complete heart block, nor are sympathomimetic drugs routinely given to this group.*

If molar sodium lactate results in the production of extrasystoles, or increases the number of ectopic beats previously present, the infusion should be discontinued. If its administration is continued beyond this point, runs of extrasystoles or ventricular tachycardia may occur. However, these usually disappear within a few minutes after the infusion is stopped. Occasionally, extrasystoles present in the control tracing are abolished by molar sodium lactate. Comparisons with epinephrine have suggested that molar sodium lactate does not tend to cause fibrillation when used in comparably effective doses and under similar conditions. Because its action is based on a different principle from that of the vagolytic and sympathomimetic drugs, it may supplement these agents and may also be effective in conditions where the others are entirely useless.

Adrenal Steroids. There is some evidence that cortisone and other adrenal steroids shorten the P-R interval and tend to accelerate A.V. conduction.[10] For example, it has been shown that the P-R interval tends to be slightly prolonged in Addison's disease and shortened in Cushing's syndrome. Moreover, cortisone has been shown to shorten A.V. conduction even when there is no manifest deficiency of adrenal steroids. The exact cause of this relationship is unknown. It has been suggested that the administration of steroids may induce alterations in the metabolism of the

junctional tissue which may increase its response to sympathetic stimulation. The effect of cortisone in lowering serum potassium may be another factor in producing these effects. Recently, Prinzmetal[11] reported an instance in which the administration of corticotropin (ACTH) tended to abolish Stokes-Adams seizures occurring in the presence of complete A.V. block.

Barium Chloride. Patients with complete A.V. heart block, who have a tendency to Stokes-Adams attacks, have been treated with barium chloride[12, 13] on the theory that the drug might prevent seizures by increasing the irritability of the idioventricular pacemaker, or developing other pacemakers. Although occasionally efficacious, this form of treatment recently has been abandoned, since barium chloride has a toxic effect on the heart and may produce multiple extrasystoles and ventricular tachycardia.

Quinidine and Procaine Amide. If the mechanism during the attack is that of multiple ventricular extrasystoles, ventricular tachycardia or ventricular flutter, the use of quinidine or procaine amide is usually considered to be contraindicated. While these agents may be successful in abolishing the arrhythmias, they will tend to depress other pacemakers and may therefore precipitate either cardiac arrest or ventricular fibrillation.

Digitalis. The use of digitalis in congestive failure accompanying complete A.V. heart block requires some comment. This complication usually indicates that the heart muscle is severely diseased. The use of digitalis in this state has been disappointing. An increase in cardiac output can occur only by increasing the output per beat (since the heart rate is fixed at a low level) and this is usually difficult to attain. Moreover, these hearts are quite vulnerable to the development of ectopic rhythms. Digitalis, by depressing the ventricular pacemakers or increasing the irritability of various foci, may produce runs of extrasystoles or Stokes-Adams attacks. Digitalis should therefore be used with caution in the presence of complete A.V. block. Massive dosage or intravenous medication should be avoided. Other measures, such as bed rest, low-salt diet, and diuretics which will not cause the above complications, are the therapy of choice in congestive failure.

Artificial Pacemaker. Cardiac arrest in animals has been successfully treated by the use of an electric pacemaker. In humans, also, heart beats have been induced by the application of an electric current across the intact chest. Zoll has reported successful resuscitation by this method in eight cases, in five of which complete recovery took place.[14] The frequency of the stimuli and the location of the electrodes determine the response. It is claimed that the artificial external pacemaker acts like a natural intracardiac parasystolic focus, except that it is under complete control. This procedure is now widely applied and its value in therapy established. We have recently observed a patient in whom the pacemaker successfully restored cardiac beating, and the heart beat could be maintained only by the use of the pacemaker; when this was removed the heart stopped on repeated trials. Molar sodium lactate given at this time restored the heart beat without the use of the pacemaker.[9]

Defibrillation. Episodes of ventricular fibrillation occurring in the Stokes-Adams syndrome have been terminated by the use of an external defibrillator which applies an electric countershock across electrodes on the chest. Zoll[15] regards the procedure as safe, practical, and rapidly effective. If defibrillation should be followed by ventricular standstill, the heart can be stimulated by the artificial cardiac pacemaker.

Thoracotomy. In repeated prolonged seizures, when none of the other measures mentioned succeed in aborting the attack, it may be necessary to perform a thoracotomy, during which cardiac massage may be applied and the heart defibrillated. We have had this procedure performed three times in a single patient. Because of the repetitive nature of these attacks, thoracotomy is indicated only in exceptional circumstances, *i.e.*, in patients with frequent attacks, when all other methods have failed to restore the heart beat.

Complications

Therapy of Numerous Extrasystoles Occurring with Complete A.V. Heart Block. The presence of numerous ventricular extrasystoles occurring in association with complete A.V. heart block presents therapeutic difficulties. In addition to complete A.V. heart block, many of these patients have one of the following complicating factors: coronary artery disease with chronic or subacute myocardial infarction, congestive heart failure, electrolyte imbalance, or some other cause of cardiac irritability. Unless the extrasystoles are the result of a transient reversible factor, the prognosis is poor since these patients manifest an increased susceptibility to ventricular tachycardia and/or ventricular fibrillation leading to a Stokes-Adams attack. One such attack may be terminal. The use of quinidine or procaine amide is contraindicated, because while these drugs may abolish the extrasystoles, they further depress the already depressed ventricular pacemakers. Sympathomimetic drugs in the form of epinephrine or Isuprel also have a tendency to increase cardiac irritability.[16] Thus, while they increase the rhythmicity of the idioventricular pacemakers, they also tend to increase the frequency of ventricular premature contractions, which may result in runs of ventricular tachycardia.[17] However, Isuprel is ap-

parently less likely to produce this complication than is epinephrine.

Cerebral Changes. The occurrence of "cerebral vascular insufficiency," due to varying degrees of systemic hypotension, often results in acute focal or generalized manifestations of cerebral dysfunction in the absence of vascular occlusion.[18] In 12 out of 25 patients with paroxysmal tachycardia, Gerard[19] found, between paroxysms, abnormalities in the electroencephalogram consisting of varying degrees of hyperexcitability. When the episodes are frequent or prolonged, irreversible cerebral changes may result, although the patient may make a complete recovery from the cardiac standpoint. We have seen several cases of this type. The therapy for the attack should be prompt and immediate (as recommended for cardiac arrest), to avoid prolonged cerebral anoxia.

Production of Apnea or Convulsions During Stokes-Adams Attacks. Attacks of ventricular asystole or ventricular fibrillation are likely to lead to apnea or convulsions.[20] Convulsions usually occur when the patient is conscious and not during coma. During cardiac standstill, continuance of respiration hyperventilates the blood in the lungs, which is transported on recovery of the heart throughout the body. The convulsions apparently begin the moment the hyperventilated blood reaches the brain. They are probably caused by the action of hyperventilated blood with its loss of CO_2 and the attendant alkaline reaction on the brain. In animal experiments, under similar conditions when oxygen and 5 per cent CO_2 were inhaled, the apnea failed to occur. However, this procedure is not recommended in the human subject. The administration of aminophylline to patients during repeated seizures seems to regulate the respirations and thus prevent episodes of apnea and convulsive seizures.

Oxygen is indicated, particularly in repeated episodes, in view of the associated anoxia; it is best given by mask or nasal catheter. The tent may be used if temperatures are high, or if the patient does not tolerate other methods.

Electrolyte Alterations. Some of these patients manifest various electrolyte disturbances. Of particular importance in therapy is the presence of a hypo- or hyperpotassemia. A slow heart rate may be induced by hyperkalemia; in such a case molar sodium lactate manifests a salutary effect.[9] In the presence of complete A.V. block, hypopotassemia may be a factor in the production of extrasystoles and the precipitation of Stokes-Adams attacks.[9, 21]

Prognosis

Death may occur in any attack; indeed this is the most common cause of death in subjects with complete A.V. heart block. The prognosis is best in those cases where the complete A.V. heart block is abolished and normal sinus rhythm is restored. The prognosis is poor in patients with repeated episodes. Penton, *et al.* (1956),[22] observed syncopal attacks in 137 out of 251 cases of complete A.V. heart block. The average duration of life after the first syncopal attack was 6.9 years (the range was several hours to 11 years). In many instances, syncope preceded complete heart block by a few months to a few years.

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